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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/809,312	03/24/2004	Lloyd A. Greene	070050.2897	6486

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EXAMINER	
MITCHELL, LAURA MCGILLEM	
ART UNIT	**PAPER NUMBER**
1636	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/809,312	GREENE ET AL.	
	Examiner	Art Unit	
	Laura M. Mitchell	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19 and 32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/31/2006, 8/18/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

It is noted that claims 1, 5, 12, 14-16 and 18-19 have been amended, claim 20-31 are cancelled and claim 32 has been added in the response filed 5/24/2007.

Claims 1-19 and 32 are under examination.

Election/Restrictions

Applicant's election without traverse of dominant negative ATF5 in the reply filed on 5/24/2007 is acknowledged.

Double Patenting

Claims 2-23 of copending Application No. 10/971,483 have been canceled and instant claims 1, 5, 12, 14-16 and 18-19 have been amended, therefore the instant claims no longer claim the same invention as claims 3-22 of copending Application No. 10/971,483. The provisional rejection of claims 1-19 under 35 U.S.C. 101 has been withdrawn.

Claim Rejections - 35 USC § 101

Claims 12, 13 and 18 have been amended to include the limitation "isolated". Therefore the rejection of claims 12, 13 and 18 under 35 U.S.C. § 101 as directed toward non-statutory subject matter is hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This is a NEW rejection.

Claim 32 is vague and indefinite because it comprises the step of transfecting a culture of neural stem or neural progenitor cells with one or more nucleic acids encoding an ATF5 inhibitor and a fluorescent protein, and the step of detecting expression of the fluorescent protein in differentiated neural cells, but it is not clear how expression of the fluorescent protein is related to differentiated neural cells. For example, it is not clear whether the nucleic acid providing the fluorescent protein is operably linked to the nucleic acid encoding an ATF5 inhibitor.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 32 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

Applicants claim a method for isolating a population of differentiated neural cells, comprising: (a) providing a culture comprising cells selected from the group consisting of neural stem cells and neural progenitor cells; (b) transfecting the culture with one or more nucleic acid, wherein said one or more nucleic acid provides an inhibitor of ATF5 and a fluorescent protein, and wherein the inhibitor is specific for ATF5, and is in an amount effective to produce differentiated neural cells; (c) detecting expression of the fluorescent protein in the differentiated neural cells; and (d) isolating the differentiated neural cells that express the fluorescent protein.

The written description requirement for a genus may be satisfied by sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that applicant was in possession of the claimed invention. Newly added claim 32 recites the limitation of "fluorescent protein" which encompasses a genus of fluorescent proteins, however the specification only provides support for eGFP in the claimed method. Therefore, the limitation of "fluorescent protein" constitutes impermissible new matter.

Claims 6, 8-11, 15, 17 and 19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one

skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This rejection is being maintained for reasons of record in the previous Office Action, mailed 4/12/2006 and for reasons outlined below.

Applicants assert that the specification provides working examples which illustrate that the claimed methods can successfully induce neural differentiation. In particular, at page 63, lines 1-30, Applicants demonstrate that the *in vitro* inhibition of ATF5 in neural progenitor cells with dominant negative ATF5 (NTAzip-ATF5), or siRNA directed toward ATF5, accelerates neurogenesis in the neuronal progenitors by specifically interfering with the function of endogenous ATF5.

Applicants submit that, with regard to claims 8-11 and 17, the method of inducing differentiation recited in independent base claims 1 and 14 is achieved *in vitro*, and transplantation of the cells is an intended use for which no threshold goal is specified. Applicants submit that there is no reason to predict that differentiation of the cell will be reversed once transplanted, or if so, in what time frame, so that transplantation of a differentiated neural cell will confer some therapeutic benefit or benefit as a research model. Applicants submit that these claims have two aspects - inducing differentiation *in vitro*, which the Examiner acknowledges is enabled, and transplantation of cells, which can be achieved using standard surgical techniques. Applicants assert that with regard to claims 6 and 15, wherein an *in vivo* neuron is contacted with an ATF5 inhibitor, the use of ATF5 specific agents such as RNAi, antisense RNA, or a dominant negative ATF5, is within the capabilities of the person skilled in the art. Applicants submit that

these techniques are accepted modes of nucleic acid delivery that the biotechnology industry continues to endorse. Applicants submit that claim 19 similarly provides for differentiation *in vitro* followed by transplantation, but in the preamble establishes the objective of the claimed method as a means to treat nervous system degeneration in a subject. Applicants submit that claim 19 is enabled because it lists a specific set of ATF5 inhibitors which belong to classes of agents which are regarded as having therapeutic benefit, as evidenced by the continued interest of the biotechnology industry. Applicants submit that it is unnecessary to demonstrate therapeutic success of the claimed invention in human trials (see M.P.E.P § 2107.03(IV); and *In re Chilowsky*, 229 F.2d 457, 461,108 USPQ 321,325(CCPA 1956) ("The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it.")).

Applicant's arguments filed 8/18/2006 have been fully considered but they are not persuasive. Although Applicants submit that the use of ATF5 specific agents such as RNAi, antisense RNA, or a dominant negative ATF5 is within the capabilities of the skilled artisan, these techniques are art-recognized as complex and relatively new techniques. The applicants have not provided sufficient guidance regarding specific dosages of any of the ATF5 inhibitors or specific information regarding *in vivo* administration to inhibit ATF5 to a subject so that a neural stem or progenitor cell would be differentiated. From the information disclosed in the specification, the skilled artisan would not know how to practice the claimed method without an excess of trial and error experimentation.

The specification has not provided specific guidance regarding how to practice the method of claim 19 to treat nervous system degeneration in a subject. The skilled artisan would not know from the instant disclosure what an effective amount of differentiated cells to administer to a subject to treat degeneration without a great deal of trial and error experimentation. Although Applicants submit that no threshold goal is specified for the transplantation methods, the specification contemplates therapeutic use of the claimed methods and claim 11 recites the limitation of a subject with nervous tissue damage. Further, the methods are drawn to transplantation of the *in vitro* differentiated cell into a human subject including an embryo. Aside from submission that standard surgical techniques can be used, the specification has not provided sufficient guidance or example regarding the number of cells that will be transplanted into a subject for any purpose including a subject with nervous tissue degeneration. The disclosure does not provide any specific guidance on how to practice the method of transplantation into an embryo, which encompasses an *in utero* procedure. The skilled artisan would not know how to practice the claimed method as the Applicants intend without excessive trial and error experimentation. Although Applicants submit that it is unnecessary to demonstrate therapeutic success of the claimed invention in human trials, it is necessary for the disclosure to provide sufficient information regarding dosages intended for human subjects and detailed information regarding administration of the therapeutic composition comprised of differentiated neural cells.

As *In re Gardner, Roe and Willey*, 427 F.2d 786,789 (C.C.P.A. 1970), the skilled artisan would eventually find out how to use the invention after "a great deal of work". In

the case of *In re Gardner, Roe and Willey*, the invention was a compound which the inventor claimed to have antidepressant activity, but was not enabled because the inventor failed to disclose how to use the invention based on insufficient disclose of effective drug dosage. The court held that "the law requires that the disclosure in the application shall inform them how to use, not how to find out how to use for themselves".

Claims 1-5, 7-8, 14 and 16-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vitro* method of promoting differentiation of a neural stem cells comprising inhibition of ATF5, does not reasonably provide enablement for an *in vivo* or *ex vivo* method of promoting differentiation of a neural stem cells comprising inhibition of ATF5 or transplanting the neural cell into a subject including humans and embryos. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. Claims 7-8 and 16-17 are newly added to this rejection.

This rejection is being maintained for reasons of record in the previous Office Action, mailed 4/12/2006 and for reasons outlined below. Applicants assert that it is not necessary for all embodiments falling within the scope of the claim be enabled. Applicants submit that for almost any claimed method, there could be unrecited conditions that would preclude successful practice of the claim. Applicants submit that for reasons set forth above, Applicants assert that the practice of the

invention *in vivo* is, in fact, enabled by the specification. Applicants submit that the specification provides working examples which show that the claimed methods practiced on neuronal stem cells and progenitors *in vitro* demonstrate effectiveness *in vivo* because said cultured neurons are accepted model systems for neurons *in vivo*.

Applicant's arguments filed 8/18/2006 have been fully considered but they are not persuasive. Although there could be unrecited conditions that would preclude successful practice of the claim for any method, the instant specification contemplates inhibition of ATF5 *in vivo* for the purpose of neural cell differentiation, which is a specific embodiment of the claim. The *in vitro* working examples combined with the guidance given in the disclosure do not provide sufficient information so that the skilled artisan would know how to practice the differentiation method *in vivo* regarding amounts of any one of the contemplated ATF-specific inhibitors (i.e. dominant negative ATF5 dosage). The *in vitro* example and the disclosure do not provide sufficient information so that the skilled artisan would know how to administer the inhibitor *in vivo* (i.e. localized injection, intravenously etc.) to any particular subject. One of ordinary skill in the art would have to perform an excessive amount of trial and error experimentation in order to determine how to practice the claimed invention in vivo. As *In re Gardner, Roe and Willey*, 427 F.2d 786,789 (C.C.P.A. 1970), the skilled artisan would eventually find out how to use the invention after "a great deal of work". In the case of *In re Gardner, Roe and Willey*, the invention was a compound which the inventor claimed to have antidepressant activity, but was not enabled because the inventor failed to disclose how to use the invention based on insufficient disclose of effective drug dosage. The court held that

"the law requires that the disclosure in the application shall inform them how to use, not how to find out how to use for themselves".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3, 7, 12, 14, 16 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Angelastro et al. Claim 5 has been amended to recite ATF5 antibody, siRNA dominant negative ATF5 and antisense RNA, and Applicants have elected the dominant negative ATF5 species. Claim 5 has been withdrawn from this rejection.

This rejection is being maintained for reasons of record in the previous Office Action, mailed 4/12/2006 and for reasons outlined below.

Applicants assert that the amended claims encompass a method of promoting neural differentiation of a neural progenitor cell by inhibiting ATF5 with an ATF5-specific inhibitor. Applicants submit that Angelastro et al does not promote neural differentiation through the specific inhibition of ATF5. As stated by the Examiner, Angelastro et al

incubates PC12 cells with NGF to promote neural differentiation, and performs SAGE analysis to determine changes in gene expression following NGF incubation. Applicants submit that as demonstrated by a class of genes that exhibit an increase in expression following NGF exposure, and a class of genes exhibiting a decrease in gene expression following NGF exposure (see page 10426, column 1, second paragraph; and table 1), NGF is not specific for ATF5. Applicants submit that Angelastro et al teaches a non-specific global affect on the NGF exposed cells wherein numerous genes may experience an increase or decrease in expression.

Applicant's arguments filed 8/18/2006 have been fully considered but they are not persuasive. Although the NGF treatment taught by Angelastro et al alters the expression of numerous other genes in PC12 cells, the limitations of the claimed methods do not exclude alteration of the expression of other genes which, absent evidence to the contrary may be occurring in a non-specific mechanism. The instant specification discloses that ATF5 may be inhibited by targeting ATF5 directly or indirectly (see paragraph 0049). The instant specification discloses that ATF5-specific agent may be any agent reactive with ATF5 protein or nucleic acid (see paragraph 0146). Since the recombinant NGF significantly decreases ATF5 expression, absent evidence to the contrary, NGF reacts with ATF5 protein or nucleic acid and meets the limitation of the claims.

Claims 12-13 and 18 are rejected under 35 U.S.C. 102(e) as being anticipated by Jessell et al (U.S. Patent Application No. 2004/0014210, filed

7/16/2002). This is a NEW rejection.

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Claim 12 is drawn to an isolated differentiated neural cell produced by the method of claim 1. Claim 13 is drawn to the differentiated neural cell which expresses eGFP. Claim 18 is drawn to an isolated population of cells comprising differentiated neural cells produced by the method of claim 14.

Jessell et al teach a method that produces differentiated neural cells that express eGFP (see paragraph 0014, for example). Absent evidence to the contrary, the cell taught by Jessell et al is the same as the instantly claimed differentiated neural cells that express eGFP and meets the limitations of claims 12-13 and 18.

These claims are drawn to a product (i.e. the cell) but the limitations of the claims are drawn to processes, and therefore are considered product-by-process claims. "[T]he lack of physical description in a product-by-process claim makes determination of the patentability of the claim more difficult, since in spite of the fact that the claim may recite only process limitations, it is the patentability of the product claimed and not of the recited process steps which must be established. We are therefore of the opinion that when the prior art discloses a product which reasonably appears to be

either identical with or only slightly different than a product claimed in a product-by-process claim, a rejection based alternatively on either section 102 or section 103 of the statute is eminently fair and acceptable. As a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith." *In re Brown*, 459 F.2d 531, 535, 173 USPQ 685, 688 (CCPA 1972). See MPEP 2113.

Because the Office does not have the facilities for examining and comparing the Applicants' product with the products of the prior art the burden is on the applicant to show a novel or unobvious difference between the claimed products and the products of the prior art (e.g. that the products of the prior art do not possess the same material structural and functional characteristics of the claimed product). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Claims 12-13 and 18 are rejected under 35 U.S.C. 102(e) as being anticipated by Yoshikazu et al (U.S. Patent Application No. 2003/0203489, filed 11/29/2002). This is a NEW rejection.

Yoshikazu et al teach cells which appeared to have differentiated into neurons that show EGFP expression (see paragraph 0170, and Figure 6, for example).

Absent evidence to the contrary, the cell taught by Yoshikazu et al is the same as the instantly claimed differentiated neural cells that express eGFP and meets the limitations of claims 12-13 and 18. These claims are drawn to a product (i.e. the cell) but

the limitations of the claims are drawn to processes, and therefore are considered product-by-process claims.

"[T]he lack of physical description in a product-by-process claim makes determination of the patentability of the claim more difficult, since in spite of the fact that the claim may recite only process limitations, it is the patentability of the product claimed and not of the recited process steps which must be established. We are therefore of the opinion that when the prior art discloses a product which reasonably appears to be either identical with or only slightly different than a product claimed in a product-by-process claim, a rejection based alternatively on either section 102 or section 103 of the statute is eminently fair and acceptable. As a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith." *In re Brown*, 459 F.2d 531, 535, 173 USPQ 685, 688 (CCPA 1972). See MPEP 2113.

Because the Office does not have the facilities for examining and comparing the Applicants' product with the products of the prior art the burden is on the applicant to show a novel or unobvious difference between the claimed products and the products of the prior art (e.g. that the products of the prior art do not possess the same material structural and functional characteristics of the claimed product). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura M. Mitchell whose telephone number is (571) 272-8783. The examiner can normally be reached on M-F 8:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Laura McGillem Mitchell, PhD
Examiner
8/6/2007

CELINE QIAN, PH.D.
PRIMARY EXAMINER